REMARKS

Claims 1, 6, 7, 13, 15, 16, 22, 24, 25, 31, 34-36, and 38 have been amended herein. Claims 11, 12, 20, 21, 29, 30, 33, and 37 were canceled in a prior response. Claims 5, 14, and 23 have been canceled herein. Such cancellation is without prejudice to further prosecution of these claims on one or more continuing applications. Claims 1-4, 6-10, 13, 15-19, 22, 24-28, 31, 32, 34-36, and 38 remain in the application. Favorable reconsideration is respectfully requested.

The claims have been amended as follows:

- The subject matter of Claim 5 has been inserted into independent Claim 1, and Claim 5 has been canceled. Claims 6 and 7 have been amended to depend directly from Claim 1.
- The subject matter of Claim 14 has been inserted into independent Claim 13, and Claim 14 has been canceled. Claims 15 and 16 have been amended to depend directly from Claim 13.
- The subject matter of Claim 23 has been inserted into independent Claim 22, and Claim 23 has been canceled. Claims 24 and 25 have been amended to depend directly from Claim 22.
- Claims 31, 34-36, and 38 have all been amended to recite that there is "one and only one" putative binding site (Claims 31 and 34) or regulatory factor binding site (Claims 35, 36, and 38), and "one and only one" anchor moiety.

The amendments recited above have verbatim support from Claims 5, 14, and 23 as originally filed.

Claims 1, 13, 22, 31, and 34 have also been amended to recite that the method excludes measuring recruitment of non-sequence specific transcriptional machinery (or excludes binding sites for transcriptional machinery in the case of Claims 31 and 34). On this point, see the Summary of the Invention in the passage starting at the bottom of page 5 and extending through the bottom of page 6. At the bottom of page 5, it is noted that regulation of transcription can be broken into many steps, two of which are (1) the sequence-specific binding of activators to genomic DNA; followed by (2) recruitment of non-sequence specific transcriptional machinery. This passage goes on to note, at the bottom of page 6, that the approach of the present invention "is **not** to measure transcription per se," but rather is to "examine closely the binding of a given regulatory factor to its **cognate nucleic acid binding site**." Emphasis added. As noted in an earlier response, the transcriptional machinery itself, which transmits the signal to RNA polymerase II to begin or end transcription, is not itself sequence-specific. See Exhibit A, which

is a brief excerpt from the website of Dr. Robert Weinzierl, a lecturer in molecular biology at the Imperial College, London, England. The transcriptional machinery "drives" transcription per se; it is the non-sequence specific "machine" that causes an activated gene to be transcribed into an mRNA molecule. The present inventive method, however, is explicitly **not** directed to measuring transcription per se, but to evaluate the mechanism of sequence-specific binding of regulatory factors to their cognate DNA binding sites.

No new matter added.

The following remarks address the issues presented in the Office Action dated November 29, 2007, in the order of their appearance.

Rejection of Claims 1-4, 7-9, 13, 16-19, 31-32, 34-36, and 38 Under §102(e) in view of Stanojevic, U.S. Patent Publication 2003/0 105 045:

As applied to Claims 1-4, 7-9, 13, and 16-19, Applicant submits that this rejection has been overcome by appropriate amendment to the claims. Specifically, the subject matter of Claim 5 has been inserted into Claim 1, and the subject matter of Claim 14 has been inserted into Claim 13. Neither Claim 5 nor Claim 14 were subject to this rejection. Thus, by inserting the subject matter of these two claims into the base independent claims (Claims 1 and 13), the independent claims are rendered free of this rejection. Dependent Claims 2-4 and 7-9 depend (directly or indirectly) from Claim 1, and dependent Claims 16-19 depend (directly or indirectly) from Claim 13. Therefore these dependent claims have also been rendered free of this rejection.

As applied to Claims 31-32, 34-36, and 38, this rejection is believed to have been overcome by amending each of these claims to require an isolated nucleic acid target that comprises "one and only one" binding site and "one and only one" anchor moiety. In making this rejection, the Office explicitly points to Fig. 6A of the Stanojevic publication, which schematically illustrates a TATA box and five (5) upstream binding sites. Claims 31-32, 34-36, and 38, however, have been amended to require "one and only one" binding site for a sequence-specific regulatory factor. Applicants thus submit that this rejection has been overcome.

In light of the amendments to the claims, Applicant respectfully submits that the §102(e) rejection in view of Stanojovic is no longer tenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-10, 13-19, 31-32, and 34 Under §103(a) over a Combination of Ansari et al. (2001) in view of Arora et al. (2002):

Applicants submit that this rejection has been overcome by appropriate amendment to independent Claims 1, 13, 31, 32, and 34.

As noted in the immediately prior section of this response, independent Claims 1, 13, 31, 32, and 34 have been amended to recite that the target nucleic acid comprises "one and only one" known binding site or putative binding site, and "one and only one" anchor. These claims have also been amended to exclude from their scope measuring recruitment of non-sequence specific transcriptional machinery (in the case of method Claims 1 and 13) and to exclude binding sites for transcriptional machinery (in the case of Claims 31 and 34). In his prior response, Applicant argued that the claims positively require that the nucleic acid target defines "a sequence-specific regulatory factor." Because transcriptional machinery is not sequence specific, went the argument, the claims are clearly distinct from the primary reference to Ansari et al. (2001). See Applicant's response filed September 4, 2007, at page 12, third full paragraph.

The Office directly addressed the point, noting that the claims as previously written "do not explicitly exclude transcriptional machinery." See the top of page 10 of the Office Action dated November 29, 2007. The specification, however, indicates that the present invention is not directed to measuring transcription per se (*i.e.*, the ultimate result of the transcription machinery) but rather is directed to a method to examine the binding of a given regulatory factor to its cognate nucleic acid binding site and to insert into the reaction, at a location proximate to where the regulatory factor binds, a test compound that is physically linked to the nucleic acid target. See page 6, last paragraph, of the application as filed. Thus, the ultimate goal of the method is not to measure the intricacies of the non-sequence-specific transcriptional machinery, but to evaluate compounds that modulate binding of a sequence-specific regulatory factor to its corresponding nucleic acid binding site. The "sequence specificity" recited in the claims thus refers to the nucleic acid sequence of the binding site in the target nucleic acid.

The distinction is briefly described in Exhibit A, which is a excerpt from the website of Dr. Robert Weinzierl, a lecturer in molecular biology at Imperial College, London. In particular, see the last paragraph of the first page of Exhibit A:

> Controlled gene expression starts by **gene-specific transcription factors binding to defined DNA sequences** near the start of transcription. A range of positive or negative regulatory signals are then passed on through numerous **protein-protein contacts with components of the transcriptional machinery**... to the ultimate recipient, RNA polymerase II.

The ultimate point being that the claims, by necessity, exclude (both specifically and implicitly) interactions with the transcriptional machinery because these interactions do not involve sequence-specific binding of a regulatory factor to its cognate DNA site.

Applicants submit that this amendment to the claims overcome the rejection in view of the combination of Ansari et al. (2001) in view of Arora et al. (2002) because Ansari et al. is limited entirely to a description of constructs that recruit elements of the transcriptional machinery. See, for example, the conclusion that is contained within the abstract of the Ansari et al. (2001) paper:

> The polyamide activator conjugates described here represent a class of DNA binding ligands which are tethered to a second functional moiety, *viz.* an activation domain, **that recruits elements of the endogenous transcriptional machinery**.

Emphasis added. The present claims, however, are not directed to probing reactions that recruit elements of the transcriptional machinery. As noted above, these elements are not sequence specific. The elements of the transcriptional machinery transmit, in a sequence-**independent** fashion, the initiation signal initially created by the binding of a sequence-specific transcription factor to a gene to RNA polymerase II.

Applicant thus submits that the combination of Ansari et al. with Arora et al. does not render obvious the claims as amended because the primary reference is limited solely to evaluating interactions with the transcriptional machinery, interactions that are excluded from the scope of the present claims.

Applicants submit that the rejection of the claims over the combination of Ansari et al. and Arora et al. has been overcome. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 22-28 Under §103(a) over a combination of Ansari et al. (2001) in view of Sadowski et al. and Arora et al. (2002):

Applicants submit that this rejection has been overcome by appropriate amendment to Claim 22, in the same fashion as noted in the immediately preceding section of this response.

Specifically, Claim 22 has been amended to exclude from its scope measuring recruitment of non-sequence specific transcriptional machinery. The claimed invention is not directed to measuring transcription per se (*i.e.*, the ultimate result of the transcription machinery) but rather is directed to a method to examine the binding of a given regulatory factor to its cognate nucleic acid binding site and to insert into the reaction, at a location proximate to where the regulatory factor binds, a test compound that is physically linked to the nucleic acid target. See page 6, last paragraph, of the application as filed. Thus, the ultimate goal of the method is not to measure or evaluate the non-sequence-specific transcriptional machinery, but to evaluate compounds that modulate binding of a sequence-specific regulatory factor to its corresponding nucleic acid binding site. The "sequence specificity" recited in the claims thus refers to the nucleic acid sequence of the binding site in the target nucleic acid.

As noted in Exhibit A, referenced earlier, controlled gene expression starts by a gene-specific transcription factor binding to a defined DNA sequence near the start of transcription. Whatever regulatory signal is generated, positive or negative, is then transmitted through numerous **protein-protein contacts with components of the transcriptional machinery**.

The claims, in contrast, explicitly exclude interactions with the transcriptional machinery because these interactions do not involve sequence-specific binding of a regulatory factor to its cognate DNA site.

Applicants submit that this amendment to the claims overcome the rejection in view of the combination of Ansari et al. (2001) in view of Sadowski et al. and Arora et al. (2002) because Ansari et al. is limited entirely to a description of constructs that recruit elements of the transcriptional machinery. See, for example, the conclusion that is contained within the abstract of the Ansari et al. (2001) paper:

> The polyamide activator conjugates described here represent a class of DNA binding ligands which are tethered to a second functional moiety, *viz.* an activation domain, **that recruits elements of the endogenous transcriptional machinery**.

Emphasis added. The present claims, however, are not directed to probing reactions that recruit elements of the transcriptional machinery. As noted above, these elements are not sequence specific. The elements of the transcriptional machinery transmit, in a sequence-**independent** fashion, the initiation signal initially created by the binding of a sequence-specific transcription factor to a gene to RNA polymerase II.

This fundamental flaw in the disclosure of the primary reference to Ansari et al. is not cured by combining the primary reference with both of Sadowski et al. and Arora et al. because both of these references are silent on the issue. Applicant thus submits that the three-way combination of Ansari et al., Sadowski et al., and Arora et al. does not render obvious the claims as amended because the primary reference is limited solely to evaluating interactions with the transcriptional machinery, interactions that are excluded from the scope of the present claims.

Applicants submit that this rejection has been overcome. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 3, 6-9, 13, and 15-18 Under §103(a) over a combination of Ansari et al. (2001), Arora et al. (2002), and Ansari et al. (2002):

Applicant submits that this rejection has been overcome by appropriate amendment to the claims. Specifically, the subject matter of Claim 5 has been inserted into Claim 1, and the subject matter of Claim 14 has been inserted into independent Claim 13. Neither Claim 5 nor Claim 14 were subject to this rejection. Thus, by inserting the subject matter of these two claims into the base independent claims (Claims 1 and 13), the independent claims are rendered free of this rejection. Dependent Claims 3 and 6-9 depend (directly or indirectly) from Claim 1, and dependent Claims 15-18 depend (directly or indirectly) from Claim 13. Therefore these dependent claims have also been rendered free of this rejection.

In light of the amendments to the claims, Applicant respectfully submits that the §103(a) rejection over Ansari et al. (2001), Arora et al. (2002), and Ansari et al. (2002) is no longer tenable. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 22 and 24-27 Under §103(a) over a combination of Ansari et al. (2001), Sadowski et al., Arora et al. (2002), and Ansari et al. (2002):

Applicant submits that this rejection has been overcome by appropriate amendment to the claims. Specifically, the subject matter of Claim 23 has been inserted into independent Claim 22. Claim 23 was not subject to this rejection. Thus, by inserting the subject matter of Claim 23 into independent Claim 22, Claim 22 is rendered free of this rejection. Claims 24-27 depend directly from Claim 22, and thus are also rendered free of this rejection by the amendment to Claim 22.

In light of the amendments to the claims, Applicant respectfully submits that the §103(a) rejection over Ansari et al. (2001), Arora et al. (2002), and Ansari et al. (2002) is no longer tenable. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendment and accompanying remarks, Applicant submits that the application is now in condition for allowance. Early notification of such action is earnestly solicited. If any questions arise, please contact the undersigned attorney. Telephone calls related to this application are welcomed and encouraged. The Commissioner is authorized to charge any fees or credit any overpayments relating to this application to deposit account number 18-2055.

Respectfully Submitted,

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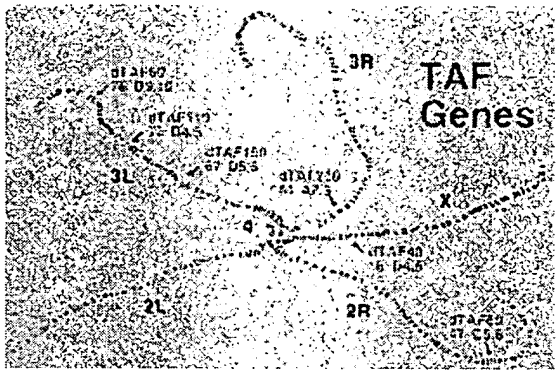
Molecular biology of the eukaryotic transcriptional machinery

Dr Robert Weinzierl (Lecturer)

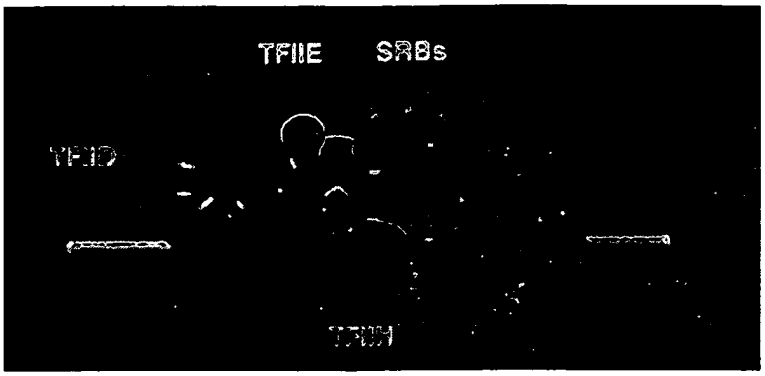


Location of coactivator (TRA)-encoding genes on Drosophila chromosomes

The primary focus of our research is to study the function of the molecules and multi-protein complexes involved in controlling the transcription of mRNAs by RNA polymerase II. Our experimental system, the fruit fly *Drosophila melanogaster*, allows us to combine a wide spectrum of techniques drawn from biochemistry, molecular biology and genetics. We anticipate that a characterization of these proteins will allow us to develop more sophisticated theories of the role of transcription in eukaryotic cell differentiation and development.

The selective expression of genes is one of the most fundamental control mechanisms governing a wide range of biological processes. Work in my laboratory focuses on the structure and function of the transcriptional machinery involved in the transcription of messenger RNAs in eukaryotic cells. This challenging and fast moving area of research aims to provide a detailed understanding of the macromolecules involved in switching genes on and off during embryonic development, cellular differentiation and in response to changing environmental conditions.

Controlled gene expression starts by gene-specific transcription factors binding to defined DNA sequences near the start sites of transcription. A range of positive or negative regulatory signals are then passed on through numerous protein-protein contacts with components of the transcriptional machinery (see figure) to the ultimate recipient, RNA polymerase II.



Schematic diagram of the RNA polymerase II Transcriptional Machinery.

In order to dissect this signal transmission pathway we use *in vitro* reconstituted transcription reactions with highly purified and well-defined components. This approach allows us to investigate systematically the functional contributions of individual components of the transcriptional machinery.

At the centre of our investigations is RNA polymerase II itself. This enzyme is not at all well understood on the biochemical level but clearly plays a major role in transcriptional control. Many, if not all of the regulatory inputs from a promoter are directed towards deciding the frequency of transcript initiation and rate of elongation. Eukaryotic RNA polymerase II consists of 12 subunits varying in size from 8 to 200 kilodaltons. These subunits may be involved in molecular contacts with other components of the basal transcriptional machinery and can thus 'sense' the regulatory information sent by gene-specific transcription factors. We are therefore very interested in studying the nature of these interactions to gain a deeper understanding of eukaryotic RNA polymerase function and how its activity is controlled during initiation and elongation of mRNAs. We have applied a number of biochemical assays to study the function of individual RNA polymerase subunits and their interactions with each other. The information obtained will eventually help us to assemble a functional enzyme *in vitro* from recombinant subunits which will allow us to recreate many key events of controlled gene expression in a completely defined system. This approach is complemented by collaboration with other groups to determine the molecular structure of several essential subunits.

Publications